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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/036,091	10/19/2001	Murali Ramachandra	16930-004610	1998

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EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 08/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Applicant 08/09/04 RS

Office Action Summary	Application No.	Applicant(s)	
	10/036,091	RAMACHANDRA, MURALI	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22,26 and 35* is/are rejected.

7)☒ Claim(s) *23-25 and 27-34* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment filed 05/24/2004 is acknowledged and entered, thereby claims 36-55 are cancelled. Claims 1-35 are pending and under consideration in this action. Any objections or rejections not repeated herein are hereby withdrawn. As new grounds of rejection or objection are set forth, **this action is NON-FINAL.**

Claim Objections

Claims 11 and 13 are objected to because of the following informalities: Each claim contains acronyms without the corresponding definition. Appropriate correction is required.

Claims 23-25 and 27-34 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. **Claims 1-12, 15-22, 26 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Green et al. (US 2002/0006661 A1; see whole document) further in view of Liu et al. (US 5,968,793; hereinafter the '793 patent; see whole document) or Yao et al. (Human Gene Ther. 1998; 9:1939-50; see whole document).**

The claims are drawn to a nucleic acid or cells comprising the nucleic acid, where the nucleic acid comprises an aptamer and a sequence encoding a transcriptional regulatory polypeptide. The ligand can be Hoechst dye 33258 or an antibiotic. The regulatory protein can be an activator, co-activator, DNA-binding domain (e.g. GAL4, tetracycline repressor). Furthermore, the nucleic acid can comprise an expression cassette within a non-viral vector.

Green et al. teach a nucleic acid and cells comprising the same, where the nucleic acids comprising an aptamer are used to control gene expression. More particularly, Green et al. teach that aptamers can be selected for with a binding specificity for a variety of small molecules (i.e. ligand), where the ligand can be an antibiotic or Hoechst dye 33258. (e.g. page 5, ¶¶ 0057, 0063). In addition, Green et al. teach an expression construct where an 33258-specific aptamer is cloned into the expression vector – PRSETA – and transformed into the 5' UTR or RSETA where addition of the ligand Hoechst 33258 (H33258) inhibits *in vitro* translation. (e.g. p. 5, ¶ 0063). Furthermore, antibiotic-specific aptamers are cloned into a non-viral expression vector PRSETA which are then transformed into bacterial cells. (e.g. p. 5, ¶ 0057). In addition, the H33258-aptamer was inserted into the 5' UTR or RSETA of a β-galactosidase expression plasmid – SVβ Gal – which are used to transfect Chinese Hamster Ovary cells (CHO). (e.g. p. 5, ¶ 0065). Green et al. state that H33342 is used, only because it is 10 times more cell-permeable but otherwise binds to the aptamer comparable to H33258. (e.g. p. 5, ¶ 0065 bridging to ¶ 0066). The nucleic acid construct is contained in a non-viral vector (SvβGal) that is used to transfect Chinese hamster ovary cells. (e.g. p. 297, col. 2 ¶ 2 through to col. 3). Green et al. teach that the gene whose expression is to be controlled can be an endogenous gene or a transgene. (e.g. p. 3, ¶ 0031). Furthermore, the gene can be in an episome such as a plasmid, a viral vector, injected as

naked DNA or can be genomic. (e.g. p. 3, ¶ 0032). Green et al. teach that the ligand can be selected from wide variety of small molecules, with the important factor being cell permeability. (e.g. p. 3, ¶ 0034; at the time of invention it was well known that aptamers could be selected with the capacity to bind virtually any class of target molecules or ligands; *See*, Jayasena, SD. Clinical Chemistry, 1999; 45(9):1628-50). Therefore, an intrinsic quality of aptamers is that they can be selected for binding specificity to any class of molecules, whether metal ion, antibiotic, interchelators or hormones.

Green et al. does not teach that the aptamer-ligand regulated gene can encode a transcriptional regulatory protein, transactivator, transcription cofactor or repressor. However, as noted above, Green et al. explicitly teaches that the gene being regulated can encode any endogenous or transgene. (e.g. p. 3, ¶¶ 0031-0032).

At the time of invention, it was well known in the art, that to regulate gene expression, one could target transcription factors (e.g. modulating their expression or functionality). For example, Yao et al. teach cell transcription fusion constructs comprising the tetracycline repressor (tetR) as a means of regulating gene expression. (e.g. Abstract; Fig. 1; showing the tetR responsive transcription switch). Alternatively, Liu et al. teach specific gene activation by chimeric GAL4 transcription factors. (e.g. Abstract; cols. 22-23, Examples 13 and 14). Liu et al. teaches that which is ubiquitously accepted in the art of gene expression – it is desirable to have the ability to regulate gene expression. (e.g. col. 1, l. 35). Each transcription factor regulates a different gene or sets of genes.

It would be obvious to modify the construct that Green et al. teaches comprising an aptamer and a polynucleotide encoding a reporter gene with the sequences encoding transcription

factors as taught by the above noted references, with the expected benefit of regulating gene expression for a gene encoding a transactivator or repressor, where different transcription factors will in turn regulate expression of target gene(s), thus expanding the arsenal of genes or phenotypic characteristics that can be studied, for example. Indeed, Green et al. teaches that the construct taught can be used to regulate expression of endogenous and transgenes. Furthermore, the cited references teach that various transcription factors, repressor and co-factors are involved in regulating of particular gene(s). At the time of the instant invention, one of skill in the art would have had a reasonable expectation of success in substituting the reporter gene as taught by Green et al. with any of the various transcription factors/repressors as taught by the above noted references.

2. **Claims 1-13, 15-22, 26 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Green et al. (US 2002/0006661 A1; see whole document) further in view of Wolffe et al. (Vitamins and Hormones, 2000 Jan; 58:449-92; see whole document).**

Additional embodiments are directed to particular repressor domains selected from a group of factors, including v-erbA. Green et al. does not explicitly teach that the regulated protein is a transcription repressor such as v-erbA.

Wolffe et al. teach that v-ErbA interacts with corepressors and represses transcription, i.e. gene expression. (e.g. p. 479, ¶ 2). For example, Wolffe et al. teach transformation defective variants of v-ErbA fail to repress transcription.

It would be obvious to modify the construct that Green et al. teaches comprising an aptamer and a polynucleotide encoding a reporter gene with the sequences encoding transcription

factors as taught by Wolffe et al., with the expected benefit of regulating gene expression for a gene encoding a transactivator or repressor, where different transcription factors will in turn regulate expression of target gene(s), thus expanding the arsenal of genes or phenotypic characteristics that can be studied, for example. Indeed, Green et al. teaches that the construct taught can be used to regulate expression of endogenous and transgenes. Furthermore, Wolffe et al. teach that various transcription factors, repressor and co-factors are involved in regulating of particular gene(s). At the time of the instant invention, one of skill in the art would have had a reasonable expectation of success in substituting the reporter gene as taught by Green et al. with any of the various transcription factors/repressors as taught by Wolffe et al.

3. **Claims 1-12, 14-22, 26 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Green et al. (US 2002/0006661 A1; see whole document) further in view of Perrem et al. (Oncogene. 1995 Oct 5;11(7):1299-307; see whole document).**

Additional embodiments are directed to particular repressor domains selected from a group of factors, including p53 protein. Green et al. does not explicitly teach that the regulated protein is a transcription repressor such as p53.

Perrem et al. teach that p53 can repress transcription from an SV40 promoter by interrupting DNA/protein complexes. (e.g. Abstract; p. 1300, Fig. 2 and Table 1).

Therefore, it would have been obvious to modify the nucleic acid that Green et al. teach by substituting the reporter gene with an endogenous or transgene encoding a transcription factor, such as p53 or any other transcription factor, coactivator, repressor or transactivator. As in any case, the gene whose expression is being regulated by the aptamer-ligand construct of

Green et al. can be a sequence encoding a gene expression modulating protein, which necessarily would itself regulate expression of a second polynucleotide sequence in a cell.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ramin (Ray) Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on Monday- Friday from 8:00-4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ray Akhavan/AU 1636

GERRY LEFFERS
PRIMARY EXAMINER